Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A method for ~~regulating a conversion rate of a hereditary trait of a~~ producing at least one high temperature resistant yeast cell, the method comprising the steps of:

~~(a) increasing~~ modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell ~~at least one DNA polymerase of the cell to higher than that of a wild type DNA polymerase~~; and

~~wherein at least two kinds of DNA polymerases playing a role in the gene replication are present, and wherein the at least two kinds of DNA polymerases have heterogeneous error-prone frequencies, and~~

~~wherein conversion of the yeast cell confers high temperature resistance to the cell;~~

~~thereby regulating the conversion rate of a hereditary trait~~

selecting and isolating the at least one high temperature resistant yeast cell, wherein the at least one high temperature resistant yeast cell exhibits a resistance to temperatures greater than temperatures tolerated by a parent yeast strain.

2. (Canceled)

3. (Withdrawn) A method according to claim 2, wherein at least about 30% of the error-prone frequency agents have a lesser error-prone frequency.

4. (Canceled)

5. (Withdrawn) A method according to claim 1, wherein the agent having the lesser error-prone frequency is substantially error-free.

6. (Currently amended) A method according to claim 1, wherein the ~~error-prone frequencies are different from each other by at least 10^1~~ step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site in the at least one DNA polymerase in a manner that increases the error-prone frequency of the at least one DNA

polymerase such that the at least one DNA polymerase provides at least one mismatched base pair in a base sequence at a rate of 10^{-6} or greater.

7. (Canceled)

8. (Canceled)

9. (Currently amended) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site in at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of ~~the at least one~~ a DNA polymerase ~~is~~ selected from the group consisting of a DNA polymerase that is innate to the at least one yeast cell and is capable of removing abnormal bases and a DNA polymerase that is innate to the at least one yeast cell and is capable of repairing mismatched base pairs~~, the DNA polymerase being present in the cell~~.

10. (Canceled)

11. (Canceled)

12. (Currently amended) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site in a DNA polymerase that has a proofreading function.

13. (Currently Amended) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of a DNA polymerase ~~comprises at least one polymerase~~ selected from the group consisting of DNA polymerase α, DNA polymerase β, DNA polymerase γ, DNA polymerase δ, and DNA polymerase ε of eukaryotic cells~~, and corresponding DNA polymerases thereto~~.

14. (Currently amended) A method according to claim 1, wherein the step of ~~regulating the error-prone frequency~~ modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises ~~regulating proofreading activity of~~ modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA

polymerase selected from the group consisting of DNA polymerase δ and DNA polymerase ε of eukaryotic cells, ~~and corresponding DNA polymerases thereto,~~ wherein modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase alters proofreading activity of the at least one DNA polymerase.

15. (Canceled)

16. (Currently amended) A method according to claim 1, wherein the ~~regulating~~ step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises introducing an exogenous DNA polymerase ~~variant~~ into the at least one yeast cell, wherein the exogenous DNA polymerase is a DNA polymerase variant having at least one modified amino acid position in a 3' to 5' exonuclease active site.

17. (Currently amended) A method according to claim 16, wherein the step of introducing the exogenous DNA polymerase ~~variant~~ into the at least one yeast cell ~~is performed with~~ comprises introducing the exogenous DNA polymerase using a method selected from ~~the group consisting of~~ homologous recombination and transformation using gene introduction or a plasmid.

18. (Canceled)

19. (Canceled)

20. (Canceled)

21. (Canceled)

22. (Canceled)

23. (Canceled)

24. (Canceled)

25. (Canceled).

26. (Canceled)

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Canceled)

31. (Canceled)

32. (Withdrawn) A method according to claim 1, wherein the cell is a mammalian cell.

33. (Currently amended) A method according to claim 1, wherein after ~~conversion of the hereditary trait~~ the step of selecting and isolating the at least one high temperature resistant yeast cell, the at least one yeast cell has substantially the same growth as that of a wild type of the at least one yeast cell.

34. (Canceled)

35. (Canceled)

36. (Currently amended) A method according to claim 1, wherein the ~~cell has at least two kinds of polymerases, one of the at least two kinds of polymerases is~~ step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a lagging strand~~, and another of the at least two kinds of polymerases is involved in an error-prone frequency of a leading strand~~.

37. (Canceled)

38. (Canceled)

39. (Withdrawn) A method according to claim 1, wherein the cell includes a cancer cell.

40. (Withdrawn) A method according to claim 1, wherein the cell constitutes a tissue.

41. (Canceled)

42. (Canceled)

43. (Canceled)

44. (Canceled)

45. (Currently Amended) A method for producing ~~a cell having a regulated hereditary trait~~ at least one high temperature resistant yeast cell, comprising the steps of:

~~(a) increasing~~ modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell ~~at least one DNA polymerase of the cell to higher than that of a wild type DNA polymerase~~, wherein the at least one DNA polymerase is selected from DNA polymerase δ and DNA polymerase ε; and

~~wherein at least two kinds of DNA polymerases playing a role in the gene replication are present, and wherein the at least two kinds of DNA polymerases have heterogeneous error-prone frequencies, and~~

~~wherein a conversion of the yeast a cell confers high temperature resistance to the cell; and~~

~~(b) reproducing the resultant cell~~ selecting and isolating the at least one high temperature resistant yeast cell, wherein the at least one high temperature resistant yeast cell exhibits a resistance to temperatures greater than temperatures tolerated by a parent yeast strain.

46. (Canceled)

47. (Canceled)

48. (Withdrawn) A method according to claim 45, wherein at least about 30% of the error-prone frequency agents have a lesser error-prone frequency.

49. (Canceled)

50. (Withdrawn) A method according to claim 45, wherein the agent having the lesser error-prone frequency is substantially error-free.

51. (Currently amended) A method according to claim 45, wherein the ~~error-prone frequencies are different from each other by at least 10^1~~ step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA

polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell such that the at least one DNA polymerase provides at least one mismatched base pair in a base sequence at a rate of 10^{-6} or greater.

52. (Canceled)

53. (Canceled)

54. (Currently amended) A method according to claim 45, wherein the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site of ~~the at least one~~ a DNA polymerase ~~is~~ selected from the group consisting of a DNA polymerase that is innate to the at least one yeast cell and is capable of removing abnormal bases and a DNA polymerase that is innate to the at least one yeast cell and is capable of repairing mismatched base pairs~~, the DNA polymerase being present in the cell~~.

55. (Currently amended) A method according to claim 45, wherein the step of ~~regulating the error-prone frequency comprises providing~~ modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site in a manner that provides a difference in the number of replication errors between one strand and the other strand of double-stranded genomic DNA in the at least one yeast cell.

56. (Canceled)

57. (Canceled)

58. (Canceled)

59. (Canceled)

60. (Canceled)

61. (Currently amended) A method according to claim 45, wherein the ~~regulating~~ step of modifying at least one amino acid position in a 3' to 5' exonuclease

active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell comprises introducing an exogenous DNA polymerase ~~variant~~ into the at least one yeast cell, wherein the exogenous DNA polymerase is a DNA polymerase variant having at least one modified amino acid position in a 3' to 5' exonuclease active site.

62. (Currently amended) A method according to claim 61, wherein the step of introducing the exogenous DNA polymerase ~~variant~~ into the at least one yeast cell ~~is performed with~~ comprises introducing the exogenous DNA polymerase using a method selected from ~~the group consisting of~~ homologous recombination and transformation using gene introduction or a plasmid.

63. (Canceled)

64. (Canceled)

65. (Canceled)

66. (Canceled)

67. (Canceled)

68. (Canceled)

69. (Canceled)

70. (Canceled)

71. (Canceled)

72. (Canceled)

73. (Canceled)

74. (Canceled)

75. (Canceled)

76. (Canceled)

77. (Withdrawn) A method according to claim 45, wherein the cell is a mammalian cell.

78. (Currently amended) A method according to claim 45, wherein after ~~conversion of the hereditary trait~~ the step of selecting and isolating the at least one high temperature resistant yeast cell, the at least one yeast cell has substantially the same growth as that of a wild type of the at least one yeast cell.

79. (Canceled)

80. (Canceled)

81. (Currently amended) A method according to claim 45, wherein the ~~cell has at least two kinds of polymerases, one of the at least two kinds of polymerases is~~ step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a lagging strand~~, and another of the at least two kinds of polymerases is involved in an error-prone frequency of a leading strand~~..

82. (Canceled)

83. (Canceled)

84. (Withdrawn) A method according to claim 45, wherein the cell includes a cancer cell.

85. (Withdrawn) A method according to claim 45, wherein the cell constitutes a tissue.

86. (Canceled)

87. (Canceled)

88. (Canceled)

89. (Canceled)

90. (Canceled)

91. (Canceled)

92. (Canceled)

93. (Canceled)

94. (Canceled)

95. (Withdrawn) A method for producing a nucleic acid molecule encoding a gene having a regulated hereditary trait, comprising the steps of:

changing an error-prone frequency of gene replication of an organism;

reproducing the resultant organism;

identifying a mutation in the organism; and producing a nucleic acid molecule encoding a gene having the identified mutation.

96. (Withdrawn) A nucleic acid molecule, produced by a method according to claim 95.

97. (Withdrawn) A method for producing a polypeptide encoded by a gene having a regulated hereditary trait, comprising the steps of: changing an error-prone frequency of gene replication of an organism; reproducing the resultant organism; identifying a mutation in the organism; and producing a polypeptide encoded by a gene having the identified mutation.

98. (Withdrawn) A polypeptide, produced by a method according to claim 97.

99. (Withdrawn) A method for producing a metabolite of an organism having a regulated hereditary trait, comprising the steps of: changing an error-prone frequency of gene replication of an organism; reproducing the resultant organism; identifying a mutation in the organism; and producing a metabolite having the identified mutation.

100. (Withdrawn) A metabolite, produced by a method according to claim 99.

101. (Withdrawn) A nucleic acid molecule for regulating a hereditary trait of an organism, comprising: a nucleic acid sequence encoding a DNA polymerase having a regulated error-prone frequency.

102. (Withdrawn) A nucleic acid molecule according to claim 101, wherein the DNA polymerase is DNA polymerase δ or ε of eukaryotic organisms, or DNA polymerase corresponding thereto of gram-positive bacteria.

103. (Withdrawn) A nucleic acid molecule according to claim 101, wherein the DNA polymerase is a variant of DNA polymerase δ or ε of eukaryotic organisms, or DNA polymerase corresponding thereto of gram-positive bacteria, the variant comprising a mutation which deletes only a proofreading activity thereof.

104. (Withdrawn) A nucleic acid molecule according to claim 101, wherein the DNA polymerase is a variant of DNA polymerase δ of eukaryotic organisms, or DNA polymerase corresponding thereto of gram-positive bacteria, the variant comprising a mutation which deletes only a proofreading activity thereof.

105. (Withdrawn) A vector, comprising a nucleic acid molecule according to claim 101.

106. (Withdrawn) A cell, comprising a nucleic acid molecule according to claim 101.

107. (Withdrawn) A cell according to claim 106, wherein the cell is a eukaryotic cell.

108. (Withdrawn) A cell according to claim 107, wherein the eukaryotic cell is selected from the group consisting of plants, animals, and yeasts.

109. (Withdrawn) A cell according to claim 106, wherein the cell is a gram-positive bacterial cell.

110. (Withdrawn) A cell according to claim 106, wherein the cell is used for regulating a conversion rate of a hereditary trait.

111. (Withdrawn) An organism, comprising a nucleic acid molecule according to claim 101.

112. (Withdrawn) A product substance, produced by a cell according to claim 106 or a part thereof.

113. (Withdrawn) A nucleic acid molecule, contained in a cell according to claim 106 or a part thereof.

114. (Withdrawn) A nucleic acid molecule according to claim 113, encoding a gene involved in the regulated hereditary trait.

115. (Withdrawn) A method for testing a drug, comprising the steps of: testing an effect of the drug using a cell according to claim 106 as a model of disease; testing an effect to the drug using a wild type of the cell as a control; and comparing the model of disease and the control.

116. (Withdrawn) A method for testing a drug, comprising the steps of: testing an effect of the drug using an organism according to claim 111 as a model of disease; testing an effect to the drug using a wild type of the organism as a control; and comparing the model of disease and the control.

117. (Withdrawn) A set of at least two kinds of polymerases for use in regulating a conversion rate of a hereditary trait of an organism, wherein the polymerases have a different error-prone frequency.

118. (Withdrawn) A set according to claim 117, wherein one of the at least two kinds of polymerases is involved in an error-prone frequency of a lagging strand, and another of the at least two kinds of polymerases is involved in an error-prone frequency of a leading strand.

119. (Withdrawn) A set according to claim 117, wherein the set of polymerases are derived from the same species.

120. (Withdrawn) A set of at /east two kinds of polymerases for use in producing an organism having a regulated hereditary trait, wherein the polymerases have a different error-prone frequency.

121. (Withdrawn) A set according to claim 120, wherein one of the at least two kinds of polymerases is involved in an error-prone frequency of a lagging strand, and another of the at least two kinds of polymerases is involved in an error-prone frequency of a leading strand.

122. (Withdrawn) A set according to claim 121, wherein the set of polymerases are derived from the same organism species.

123. (Withdrawn) Use of at least two kinds of polymerases for regulating a conversion rate of a hereditary trait of an organism, wherein the polymerases have a different error-prone frequency.

124. (Withdrawn) Use of at least two kinds of polymerases for producing an organism having a regulated hereditary trait, wherein the polymerases have a different error-prone frequency.

125. (Withdrawn) A method for regulating a conversion rate of a hereditary trait of a yeast cell, wherein the cell has resistance to temperature, the resistance not being possessed by the cell before the conversion, the method comprising the steps of:

regulating the proofreading function of at least one DNA polymerase of the yeast by site-directed mutagenesis; and

subjecting the yeast to acclimation culture by gradually increasing culture temperature.

126. (New) A method for producing at least one high temperature resistant yeast cell, comprising the steps of:

modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell in a manner that increases the error-prone frequency of DNA replication in the at least one yeast cell such that the at least one DNA polymerase provides at least one mismatched base pair in a base sequence at a rate of 10^{-6} or greater, wherein the at least one DNA polymerase is selected from DNA polymerase δ and DNA polymerase ε; and

selecting and isolating the at least one high temperature resistant yeast cell, wherein the at least one high temperature resistant yeast cell exhibits a resistance to temperatures greater than temperatures tolerated by a parent yeast strain.

127. (New) A method according to claim 126, further comprising, restoring the error prone frequency of DNA replication in the at least one yeast cell to an error prone frequency exhibited during DNA replication in the at least one yeast cell prior to the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase.

128. (New) A method according to claim 1, further comprising, restoring the error prone frequency of DNA replication in the at least one yeast cell to an error prone frequency exhibited during DNA replication in the at least one yeast cell prior to the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase.

129. (New) A method according to claim 45, further comprising, restoring the error prone frequency of DNA replication in the at least one yeast cell to an error prone frequency exhibited during DNA replication in the at least one yeast cell prior to the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase.

130. (New) A method for producing a desired hereditary trait in at least one eukaryotic cell, the method comprising the steps of:

modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell in a manner that increases the error-prone frequency of DNA replication in the at least one eukaryotic cell; and

selecting and isolating the at least one eukaryotic cell exhibiting the desired hereditary trait.

131. (New) The method of claim 130, wherein the at least one eukaryotic cell is selected from a yeast cell, a mammalian cell, an embryonic stem cell, a tissue, an organism, and a mouse.

132. (New) A method according to claim 131, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell in a manner that increases the error-prone frequency of DNA replication in the at least one eukaryotic cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase in a manner that increases the error-prone frequency of the at least one DNA polymerase such that the at least one DNA polymerase provides at least one mismatched base pair in a base sequence at a rate of 10^{-6} or greater.

133. (New) A method according to claim 131, wherein the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase operable in at least one eukaryotic cell in a manner that increases the error-prone frequency of DNA replication in the at least one eukaryotic cell comprises modifying at least one amino acid position in the 3' to 5' exonuclease active site of a DNA polymerase selected from the group consisting of a DNA polymerase that is innate to the at least one eukaryotic cell and is capable of removing abnormal bases and a

DNA polymerase that is innate to the at least one eukaryotic cell and is capable of repairing mismatched base pairs.

134. (New) A method according to claim 132, A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a lagging strand.

135. (New) A method according to claim 132, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site in at least one DNA polymerase operable in at least one eukaryotic cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site in a DNA polymerase that has a proofreading function.

136. (New) A method according to claim 132, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of a DNA polymerase selected

from the group consisting of DNA polymerase α, DNA polymerase β, DNA polymerase γ, DNA polymerase δ, and DNA polymerase ε of eukaryotic cells.

137. (New) A method according to claim 132, wherein the step modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell in a manner that increases the error-prone frequency of the at least one DNA polymerase comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase selected from the group consisting of DNA polymerase δ and DNA polymerase ε of eukaryotic cells, wherein modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase alters proofreading activity of the at least one DNA polymerase.

138. (New) A method according to claim 132, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell in a manner that increases the error-prone frequency of DNA replication in the at least one eukaryotic cell comprises introducing an exogenous DNA polymerase into the at least one eukaryotic cell, wherein the exogenous DNA polymerase is a DNA polymerase variant having at least one modified amino acid position in a 3' to 5' exonuclease active site.

139. (New) A method according to claim 138, wherein the step of introducing the exogenous DNA polymerase into the at least one eukaryotic cell comprises introducing the exogenous DNA polymerase using a method selected homologous recombination and transformation using gene introduction or a plasmid.

140. (New) A method according to claim 138, wherein the step of introducing an exogenous DNA polymerase variant comprises introducing a DNA polymerase variant selected from a DNA polymerase variant derived from a species of eukaryotic organism that is the same as the at least one eukaryotic cell and a DNA polymerase variant derived from a species of eukaryotic organism that is different from the at least one eukaryotic cell.

141. (New) A method according to claim 16, wherein the step of introducing an exogenous DNA polymerase variant comprises introducing a DNA polymerase variant selected from a DNA polymerase variant derived from a species of yeast that is the same as the at least one yeast cell and a DNA polymerase variant derived from a species of eukaryotic organism that is different from the at least one yeast cell.

142. (New) A method according to claim 61, wherein the step of introducing an exogenous DNA polymerase variant comprises introducing a DNA polymerase variant selected from a DNA polymerase variant derived from a species of yeast that is the

same as the at least one yeast cell and a DNA polymerase variant derived from a species of eukaryotic organism that is different from the at least one yeast cell.

143. (New) A method according to claim 1, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a leading strand.

144. (New) A method according to claim 45, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one yeast cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a leading strand.

145. (New) A method according to claim 132, wherein the step of modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase operable in at least one eukaryotic cell comprises modifying at least one amino acid position in a 3' to 5' exonuclease active site of at least one DNA polymerase involved in an error-prone frequency of a leading strand.

146. (New) A method according to claim 130, further comprising, restoring the error prone frequency of DNA replication in the at least one eukaryotic cell to an error prone frequency exhibited during DNA replication in the at least one eukaryotic cell prior to the step of modifying at least one amino acid position in the 3' to 5' exonuclease active site of the at least one DNA polymerase.